(SOME) APPLICATIONS OF THE MEDIPIX AND TIMEPIX ASICS IN LIFE SCIENCE AND BIOLOGY

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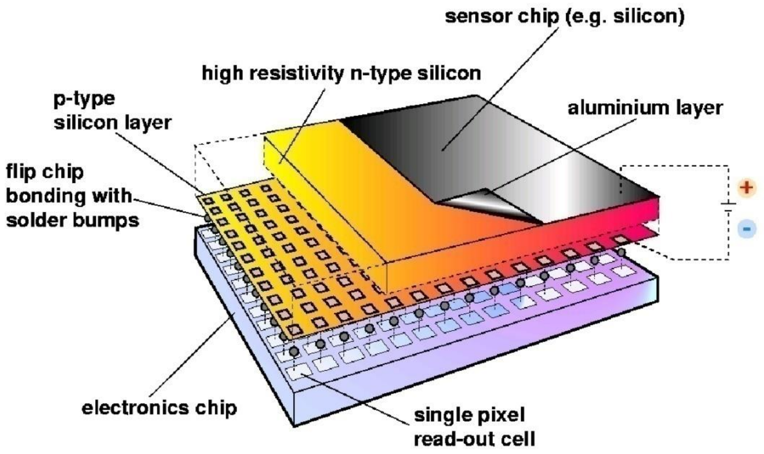
[1] Honorary Professor at Glasgow University

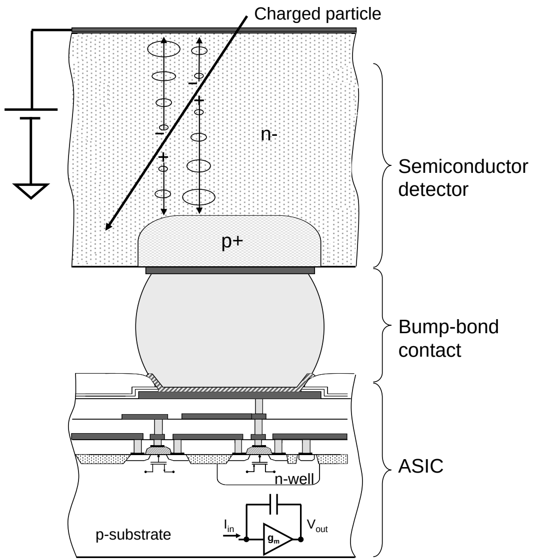
Medipix2 (1999 ->)	Medipix3 (2005 ->)	Medipix4 (2016 ->)
Albert-Ludwig Universität Freiburg, Germany	Albert-Ludwig Universität Freiburg, Germany	CEA, Paris, France
CEA, Paris, France	AMOLF, Amsterdam, The Netherlands	CERN, Geneva, Switzerland
CERN, Geneva, Switzerland	Brazilian Light Source, Campinas, Brazil	DESY-Hamburg, Germany
Czech Academy of Sciences, Prague, Czechia	CEA, Paris, France	Diamond Light Source, England, UK
ESRF, Grenoble, France	CERN, Geneva, Switzerland	IEAP, Czech Technical University, Prague, Czeciah
IEAP, Czech Technical University, Prague, Czech Republic	DESY-Hamburg, Germany	IFAE, Barcelona, Spain
IFAE, Barcelona, Spain	Diamond Light Source, England, UK	JINR, Dubna, Russian Federation
Mid Sweden University, Sundsvall, Sweden	ESRF, Grenoble, France	NIKHEF, Amsterdam, The Netherlands
MRC-LMB Cambridge, England, UK	IEAP, Czech Technical University, Prague, Czech Republic	University of California, Berkeley, USA
NIKHEF, Amsterdam, The Netherlands	KIT/ANKA, Forschungszentrum Karlsruhe, Germany	University of Canterbury, Christchurch, New Zealand
University of California, Berkeley, USA	Mid Sweden University, Sundsvall, Sweden	University of Geneva, Switzerland
Universität Erlangen-Nurnberg, Erlangen, German	NIKHEF, Amsterdam, The Netherlands	University of Glasgow, Scotland, UK
University of Glasgow, Scotland, UK	Univesridad de los Andes, Bogota, Columbia	University of Houston, USA
University of Houston, USA	University of Bonn, Germany	University of Maastricht, The Netherlands
University and INFN Section of Cagliari, Italy	University of California, Berkeley, USA	University of Oxford, England, UK
University and INFN Section of Pisa, Italy	University of Canterbury, Christchurch, New Zealand	INFN, Italy
University and INFN Section of Napoli, Italy	Universität Erlangen-Nurnberg, Erlangen, German	
	University of Glasgow, Scotland, UK	
	University of Houston, USA	
	University of Leiden, The Netherlands	
	Technical University of Munich, Germany	
	VTT Information Technology, Espoo, Finland	

Acknowledgements – Commercial Partners

COLLABORATION NAME	Medipix2			Medipix3		Medipix4	
ASICS	**Medipix2**	**Timepix**	**Timepix2**	**Medipix3**	**Timepix3**	**Medipix4**	**Timepix4**
ADVACAM s.r.o., Czech Republic	X	X	X	X	X		
Amsterdam Scientific Instruments, The Netherlands	X	X	X	X	X		
Kromek, UK	X	X	X				
Malvern-Panalytical, The Netherlands	X	X	X	X			
MARS Bio Imaging, New Zealand				X			
Pitec, Brasil				X			
Quantum Detectors, UK				X			
X-ray Imaging Europe, Germany	X	X	X				
X-spectrum, Germany				X			

Hybrid Silicon Pixel Detectors





- Noise-hit free images possible (high ratio of threshold/noise)
- Standard CMOS can be used allowing on-pixel signal processing
- Sensor material can be changed (Si, GaAs, CdTe..)
- Semiconductor sensor can be replaced by a gas gain grid or MCP

Outline

- Medipix3
- Spectroscopic imaging in medicine
- TEM , STEM and Cyro-EM
- Timepix3
- Imaging Time of Flight mass spectrometry
- Thyropix – single chip SPECT
- Timepix4 and Medipix4
- Looking further ahead

What if...

- Each pixel counted incoming hits to make an image?
- Each pixel measured the charge of those hits?
- Could we make ‘colour’ X-ray images?
- This led to the Medipix chip family

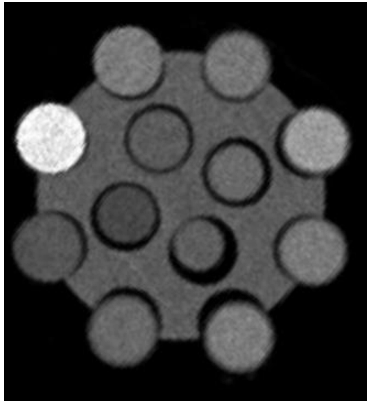
Medipix3 chip for high rate spectroscopic X-ray imaging

- Collaboration started in 2005
- Large matrix (256 x 256) with fine pixel pitch (55μm)
- Selectable sensor pixel pitch (55μm or 110μm)
- Inter-pixel charge summing logic > mitigate charge sharing in sensor
- Up to 8 counters per (110μm) pixel
- Camera logic (open shutter > count > close shutter > read out image)
- Possibility of continuous read/write

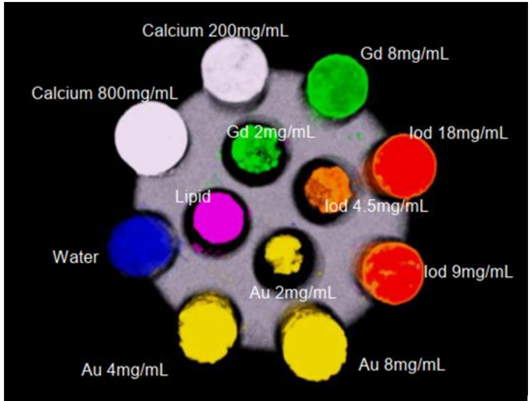
Material	N	k-edge (keV)	$K\alpha$ energy (keV)	$d\alpha$ (μm)	η [%]
Si	14	1.84	1.74	12	5
Ge	32	11.11	9.89	51	55
GaAs:					
Ga	31	10.38	9.25	42	51
As	33	11.87	10.54	16	57
CdTe:					
Cd	48	26.73	23.17	128	84
Te	52	31.82	27.47	64	87

Grayscale to Material Imaging

- Spectral imaging using Medipix3RX allows you to identify and quantify different materials
  - a separate map (data channel) is made for each material
  - each map gives the partial density (g/cm^3) for the material
  - each material is then assigned a colour for easy visualisation



Single Energy detector



MARS Spectral detector

A phantom containing Au, Gd, iodine, lipid, water and hydroxyapatite

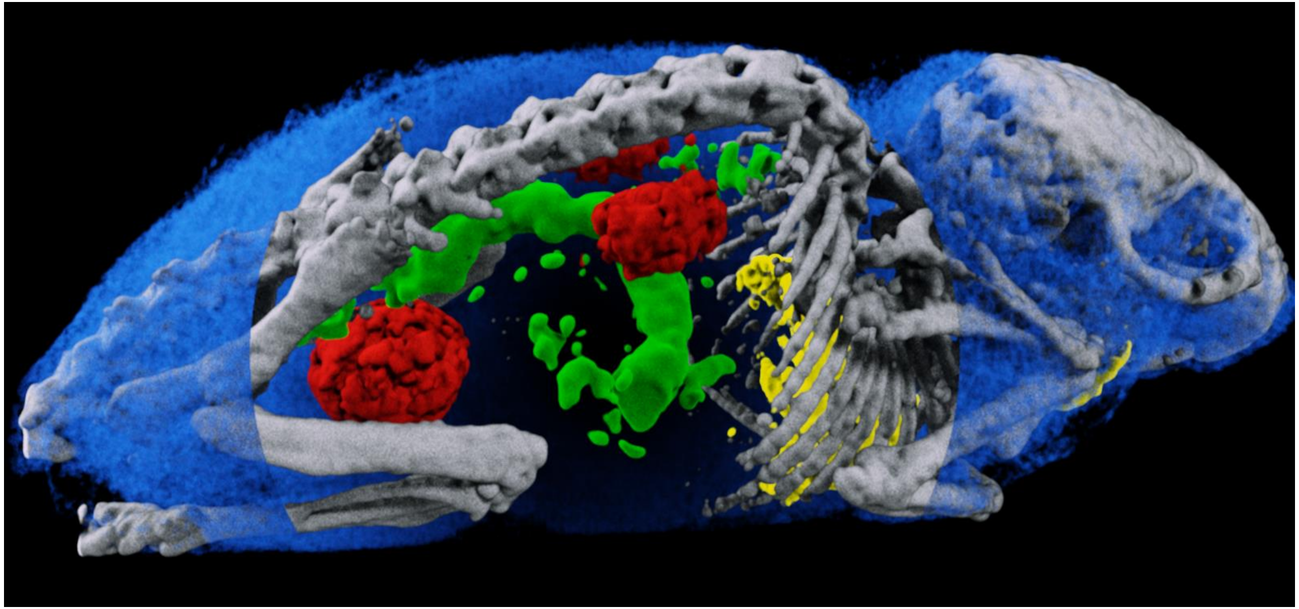
https://www.marsbioimaging.com/mars/

MARS small animal scanner

Notre Dame imaging lab

Slide courtesy of A. Butler, University of Canterbury

First material separation small animal image



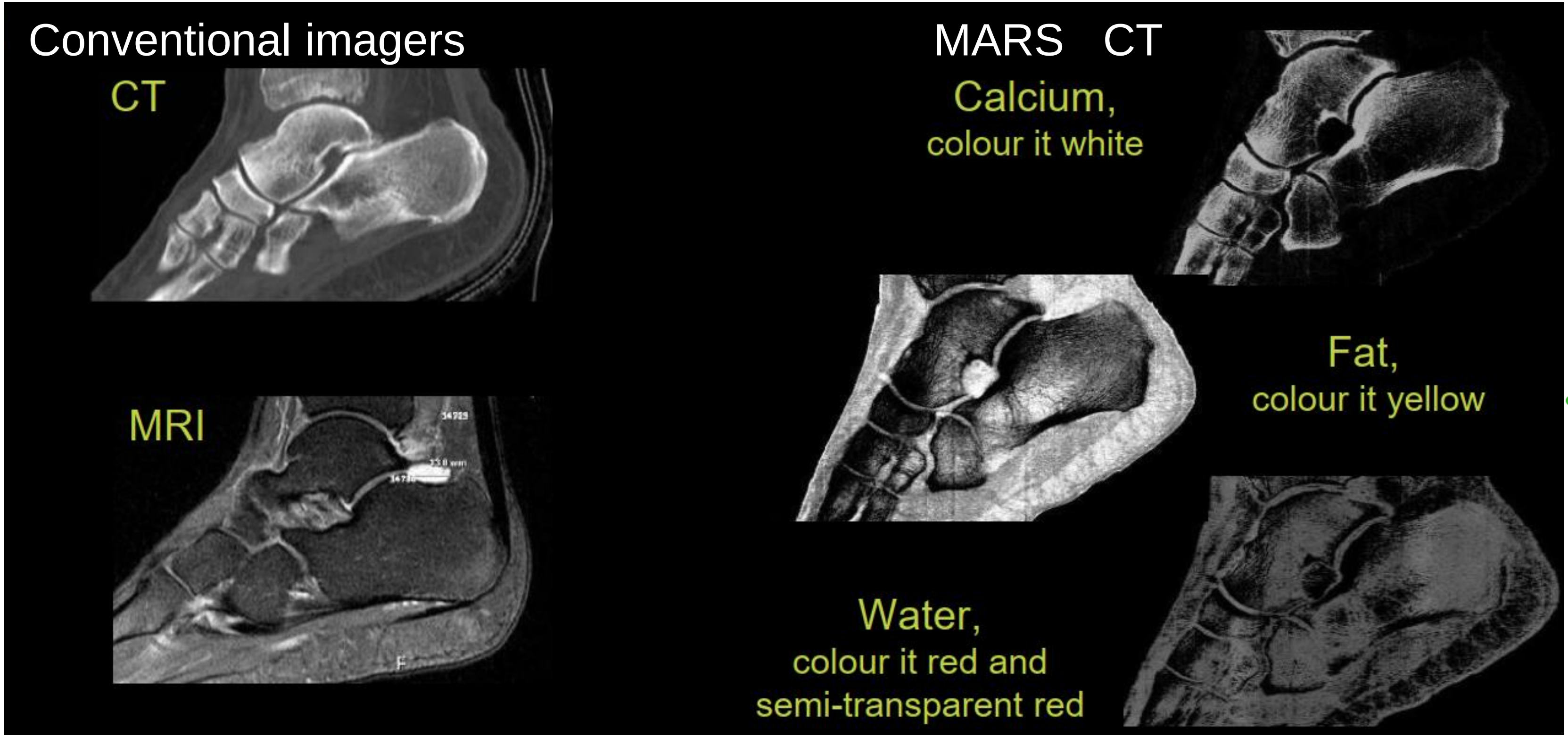
The water has been partly cut away to reveal the bone, gold, gadolinium and iodine

Here the metals are used as contrast agents. The big quesstion is whether we can develop and image bio-markers for functional imaging (replacing PET is some circumstances).

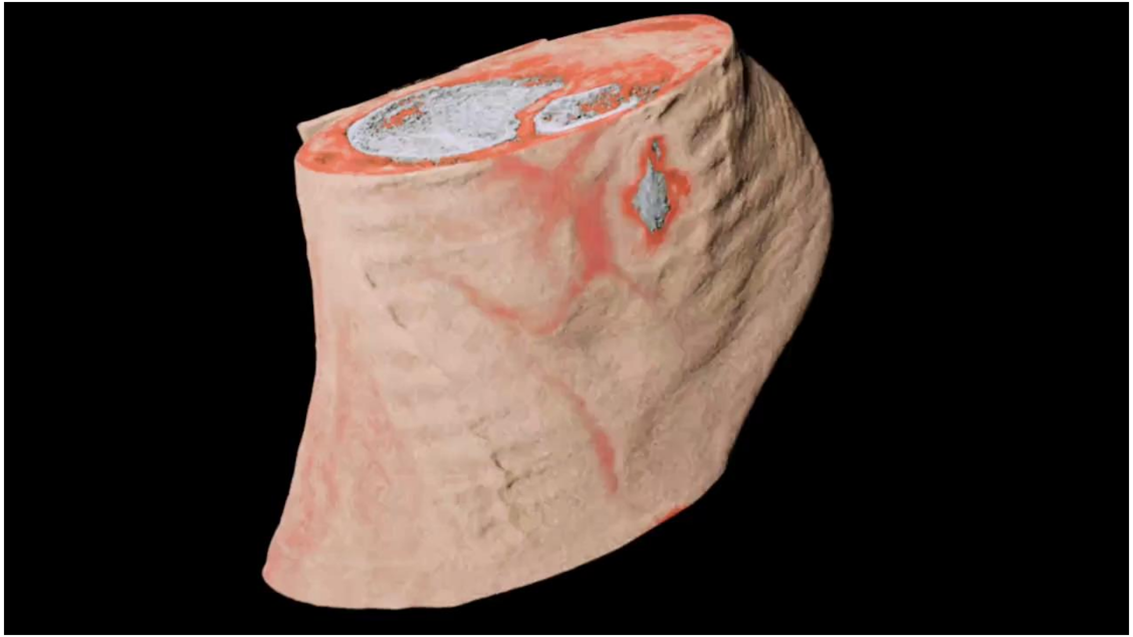
First living human scan…

Phil Butler, CEO of MARS Bio Imaging

Slice through Phil's ankle



Movie Slice through Phil's ankle



Press Impact

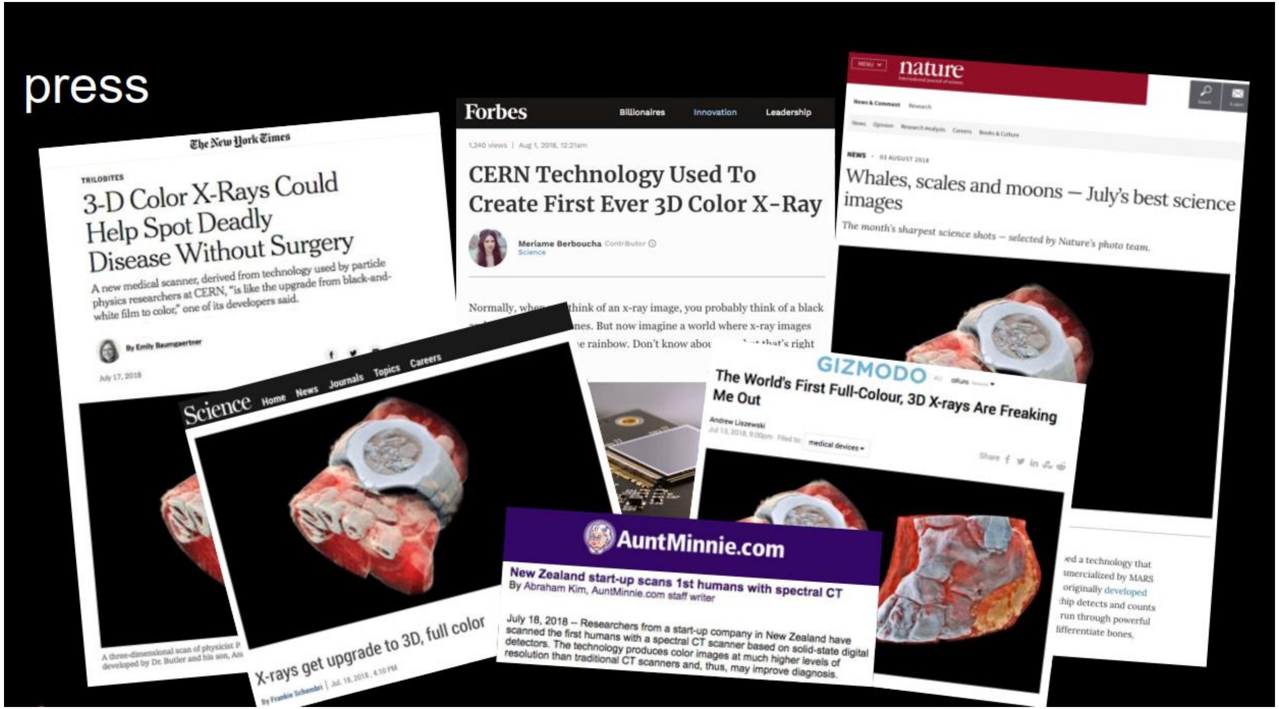


Image viewed over 40 M times on Twitter

Highest number of hits on CERN website since the Higgs announcement

MARS scan of diseased carotid artery

CERN Accelerating science

Knowledge Transfer
Accelerating Innovation

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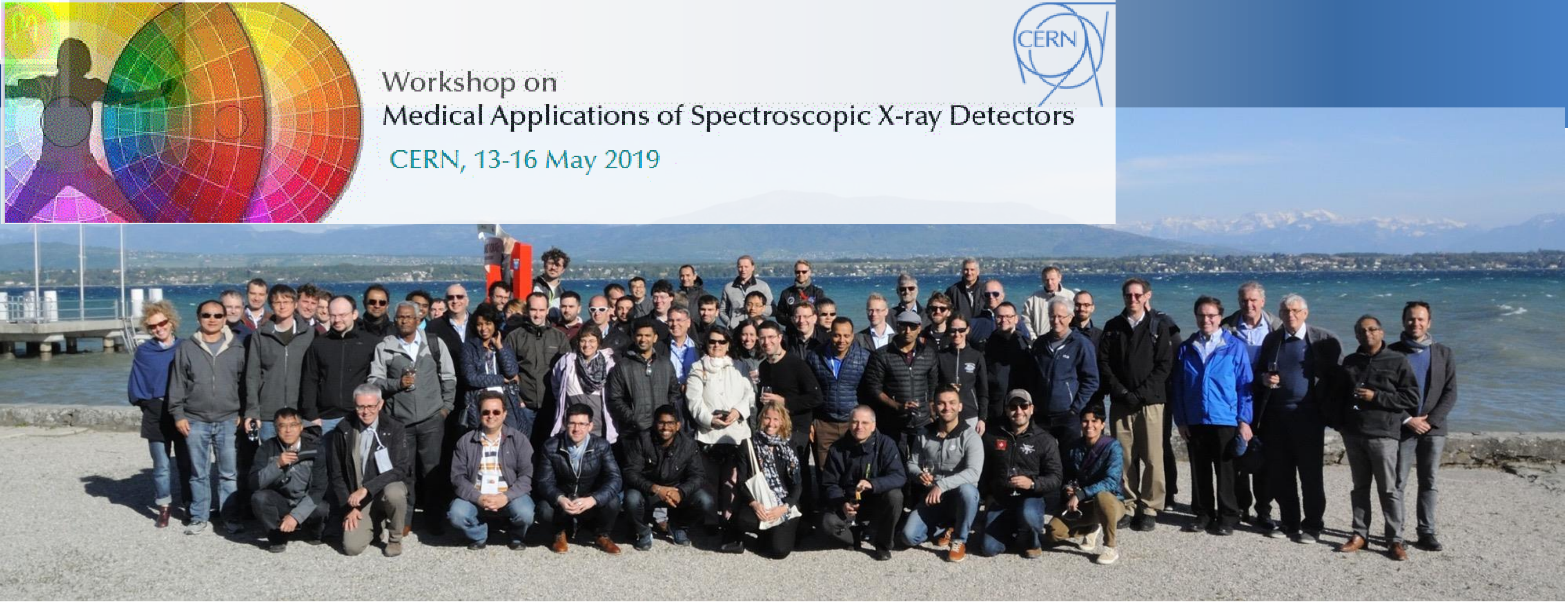
News › › News › Topic: Knowledge sharing

First European hospital receives 3D colour X-ray scanner using CERN technology

MARS Bioimaging's 3D colour X-ray scanner has arrived in Europe to undertake clinical trials that will lead to its medical use.

22 JUNE, 2021 | By Antoine Le Gall

MARS Bioimaging scanner at Lausanne University Hospital (CHUV). (Image: CHUV)



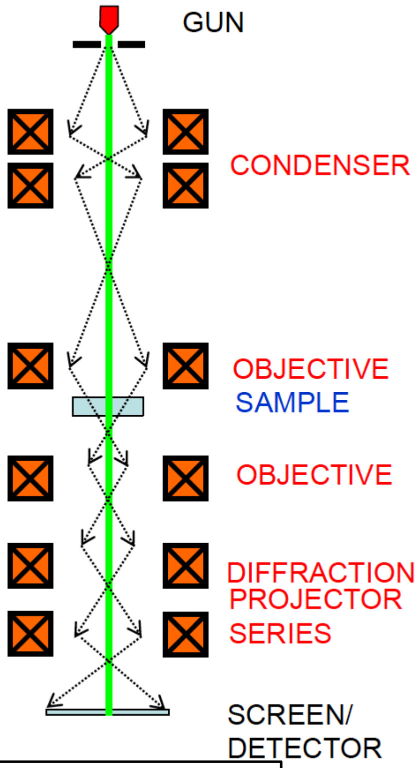
~120 invited participants of which ~50 were from industry

All large medical equipment suppliers represented: Canon, GE, Philips, Siemens

Also major research institutes present :Johns Hopkins, Massachusetts General Hospital, Mayo Clinic, Royal Marsden, TU Munich etc

Medipix Collaboration plays a ‘pathfinding’ role in this community

TEM, STEM and cryo-EM



Electrons -
60-300 keV kinetic energy
5 to 2 picometres wavelength

High vacuum in column

Modes -
TEM – Condenser illuminates, Objective magnifies
STEM – Condenser/Objective focuses probe, beam scanned

Sample rods, multiple functions
Sample thickness required < 100 nm

Traditional detectors:
TEM – Imaging camera – CCD or CMOS
STEM – scintillator:PMT solid, annular
DPC segmented pn diodes

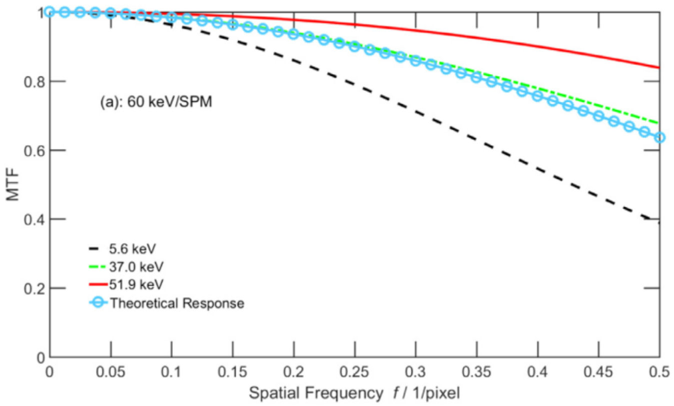
Courtesy of D. M^c^Grouther, Glasgow

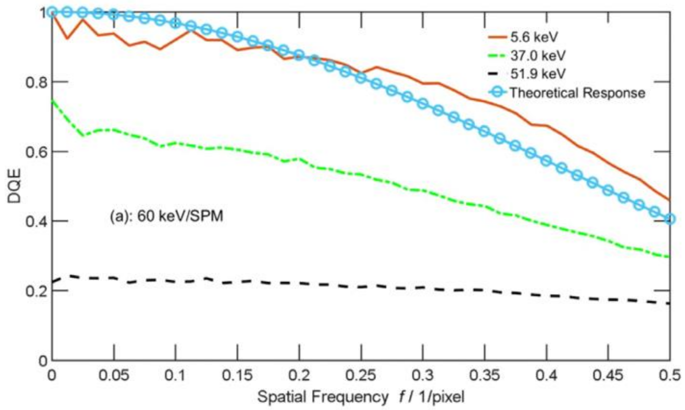
Kelvin Nanocharacterisation Centre

Detection of 60keV electrons (300μm thick Si)

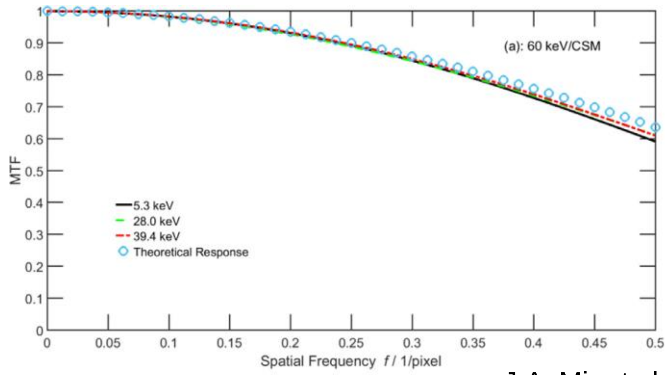
Modulation Tranfer Function

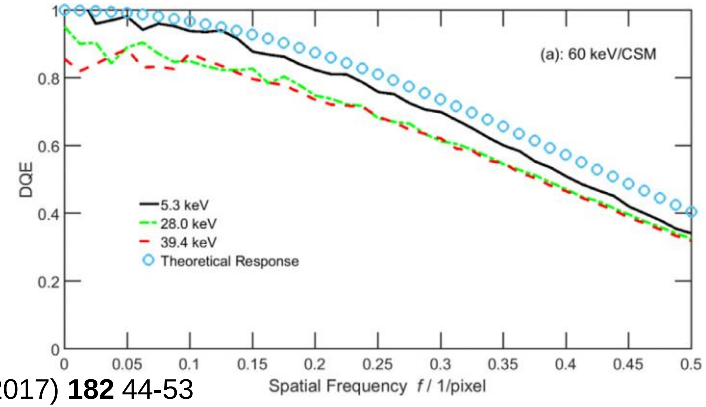
Detective Quantum Efficiency





Single Pixel Mode





Charge Summing Mode

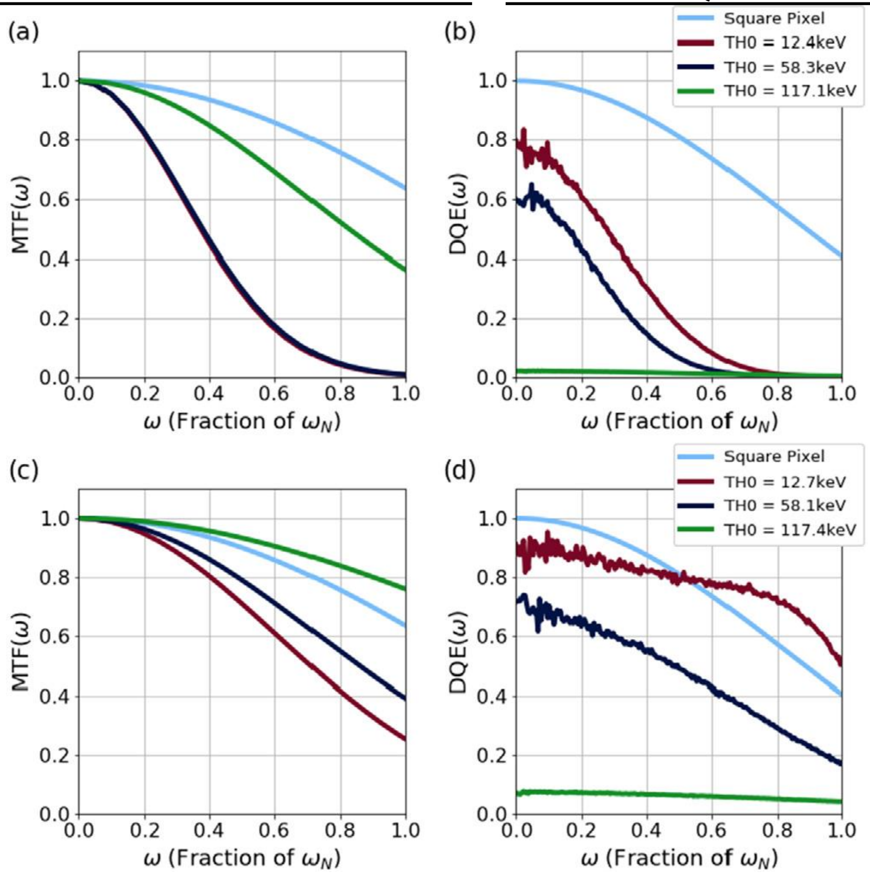
J.A. Mir et al., Ultramicroscopy (2017) **182** 44-53

Detection of 120keV electrons (300μm thick GaAs)

Modulation Tranfer Function | Detective Quantum Efficiency

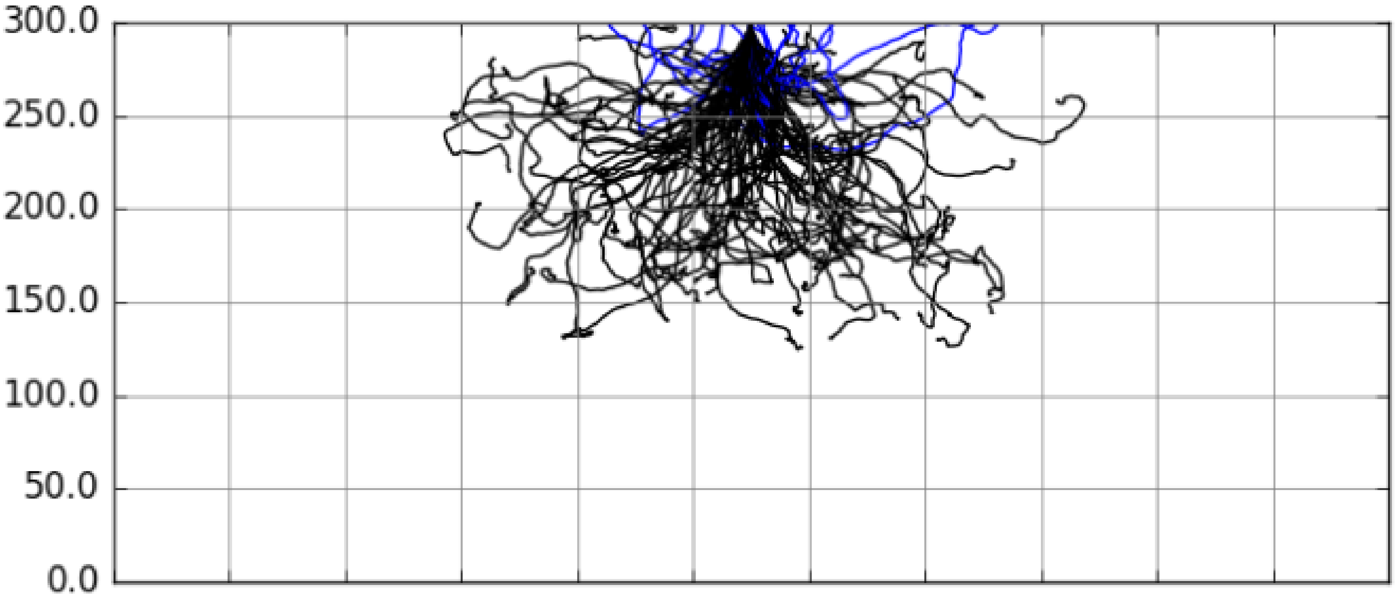
Single Pixel Mode

Charge Summing Mode



Kirsty A. Paton et al., Ultramicroscopy (2021) **227** 113298

Simulation of 200keV electron impinging on 300μm thick Si



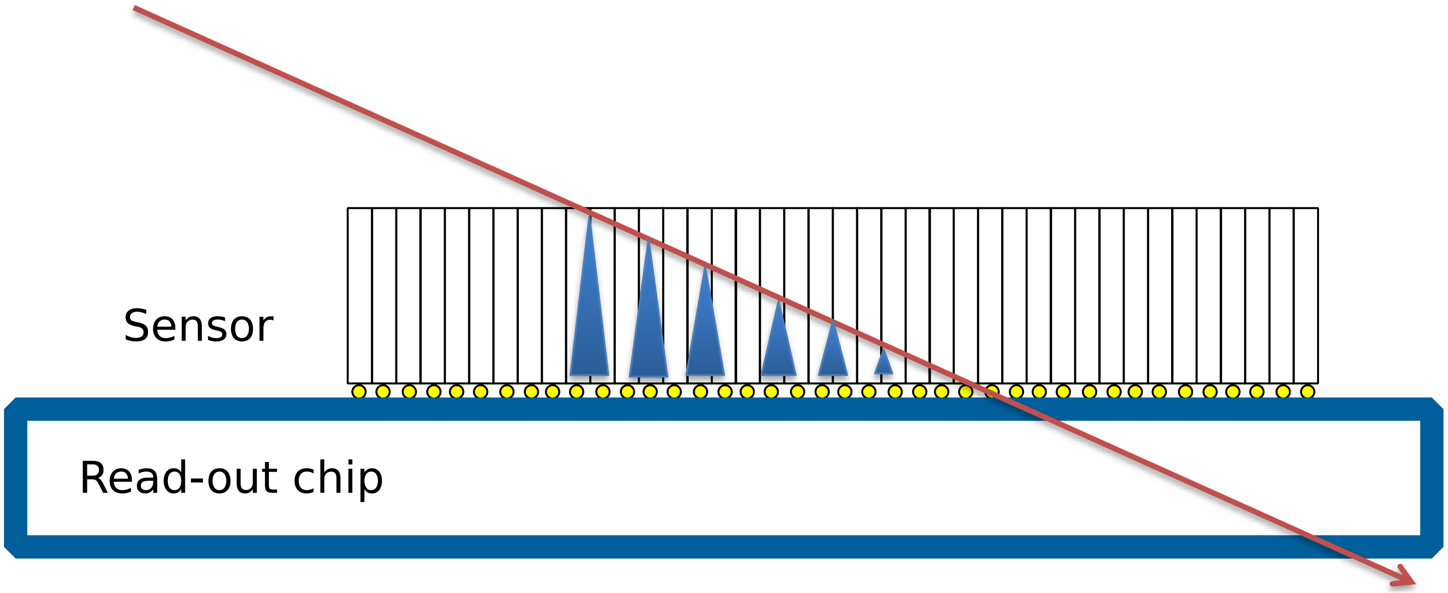
Courtesy of J. P. van Schayck, Maastricht

Timepix3 – single particle detection

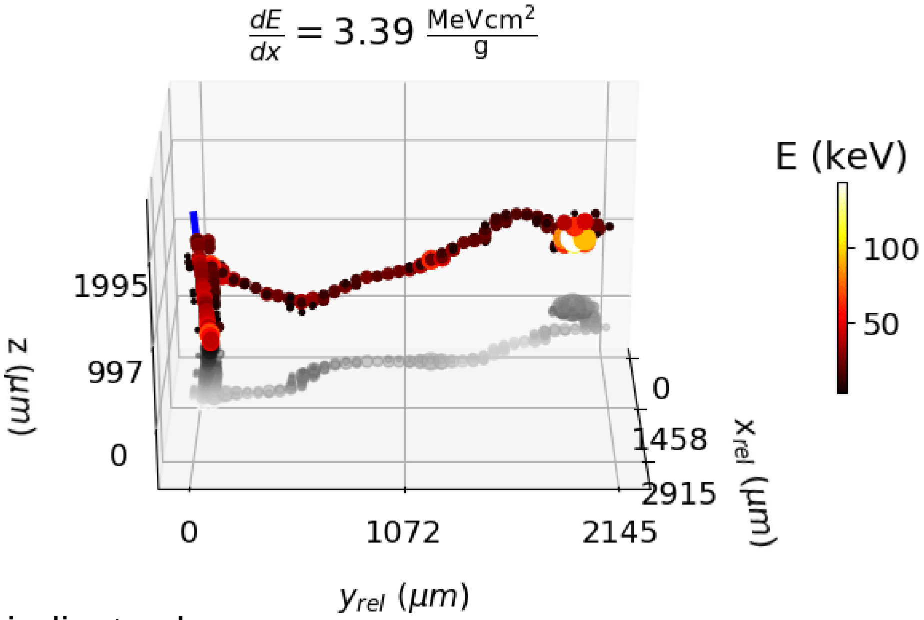
CMOS node	130nm
Pixel Array	256 x 256
Pixel pitch	55μm
Charge collection	e^-, h^+
Pixel functionality	TOT (Energy) and TOA (Arrival time)
Preamp Gain	~47mV/ke^-
ENC	~60e^-
FE Linearity	Up to 12ke^-
TOT linearity (resolution)	Up to 200ke^- (<5%)
TOA resolution*	Down to 1.6ns
Time-walk	<20ns
Minimum detectable charge	~500e^- → 2 KeV (Si Sensor)
Power power (1.5V)	700 mW/cm^2
Maximum hit rate	80Mhits/cm^2/sec (in data driven)
Readout	Data driven (44-bits/hit @ 5Gbps)

* Thanks to V. Gromov, et al. Nikhef, C. Brezina et al., Bonn

Using charge collection time to track in a single Si layer



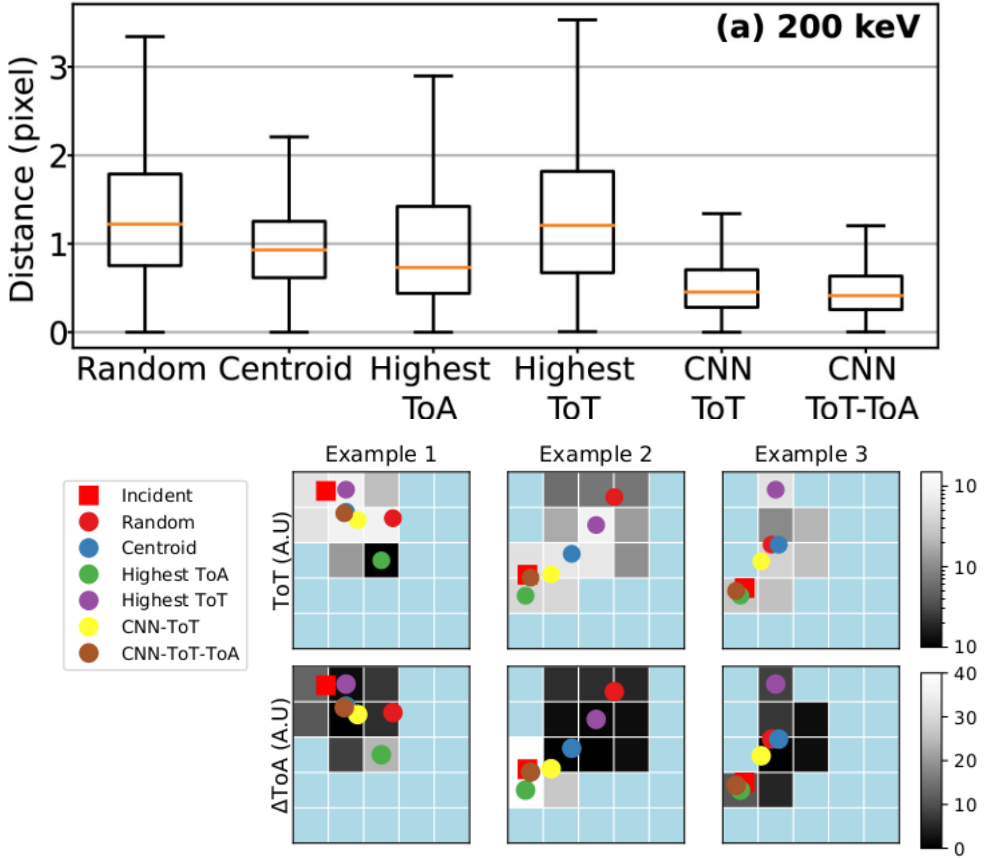
3D rendering of traversing particle with delta electron



45 deg
CdTe sensor
2mm thick
V_{bias} = 130V
Colour (and diameter) indicate charge

Slide courtesy of B. Bergmann, S. Pospisil, IEAP, CTU, Prague

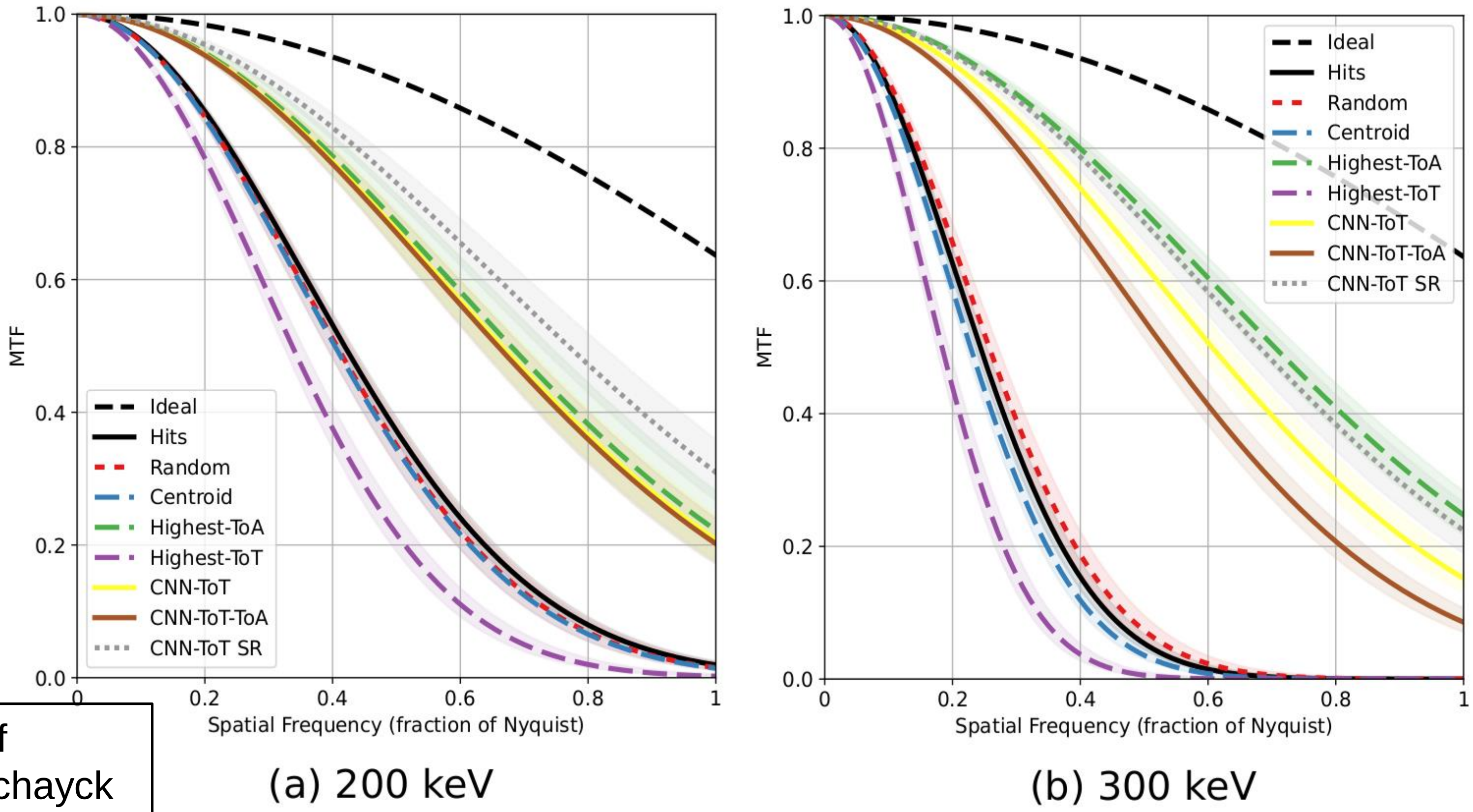
Use simulated data to train a CNN to identify impact point



Courtesy of
J. P. van Schayck
Maastricht

J. Paul van Schayck et al., Ultramicroscopy (2020) **218** 113092

Comparison of the performance of different algorithms



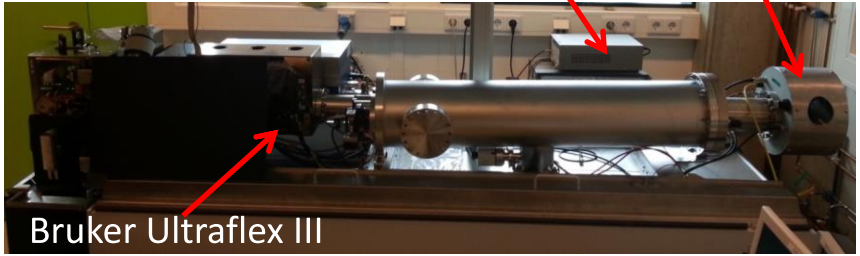
Courtesy of
J. P. van Schayck
Maastricht

J. Paul van Schayck et al., Ultramicroscopy (2020) **218** 113092

Mass spectrometry enhanced with segmented Timepix MCP Readout

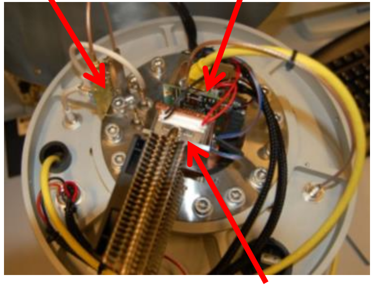
Delay generator and MCP power supplies

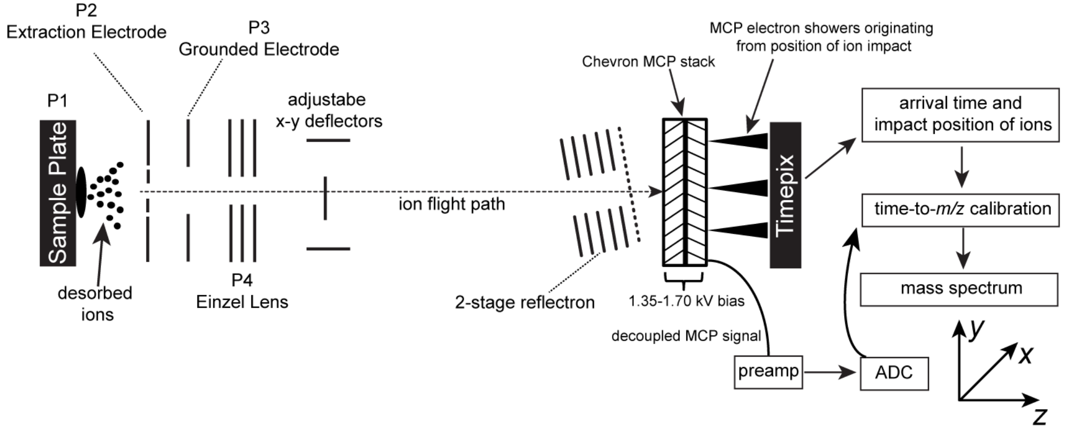
Timepix assembly



MCP decoupling

ReLaXd readout board

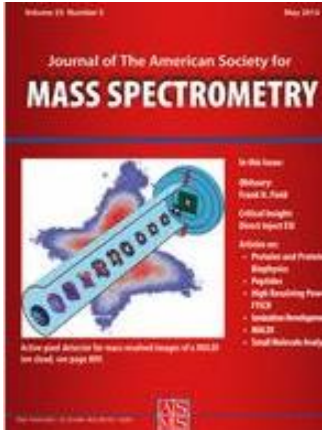




Two spectra per laser shot:

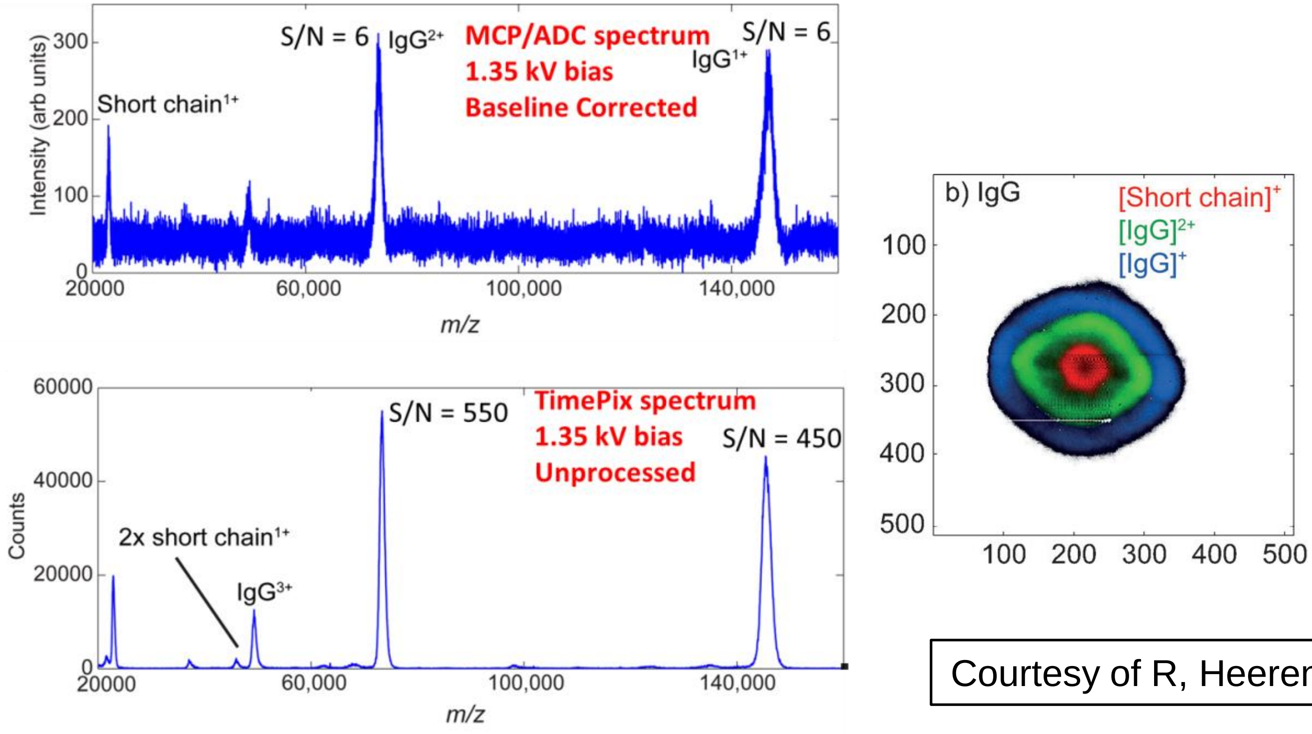
1- Timepix (position and time)

2- ADC (time, multihit)



Ellis et al. J. Am. Soc. Mass Spec. (2014) **25** 809-819

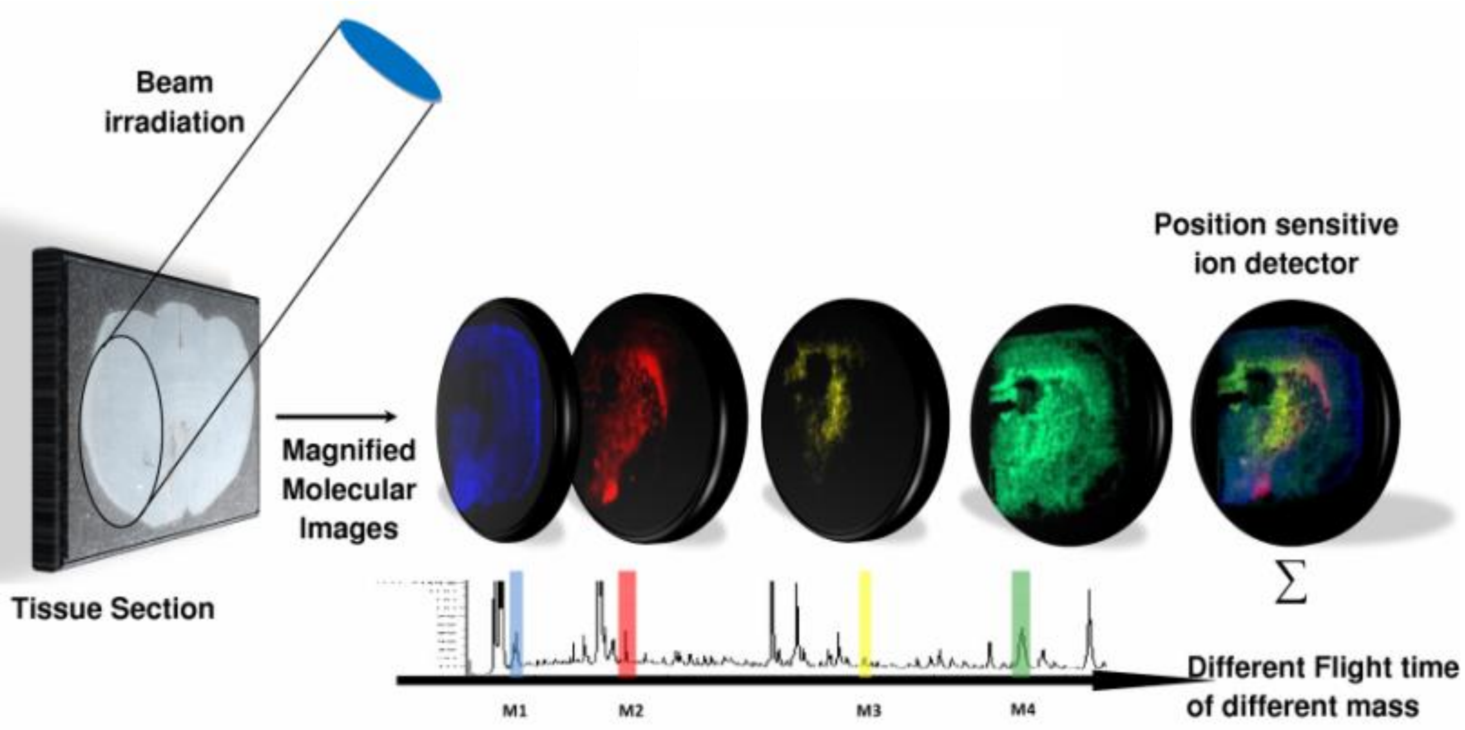
Improved High Mass Sensitivity



Courtesy of R, Heeren, Maastricht

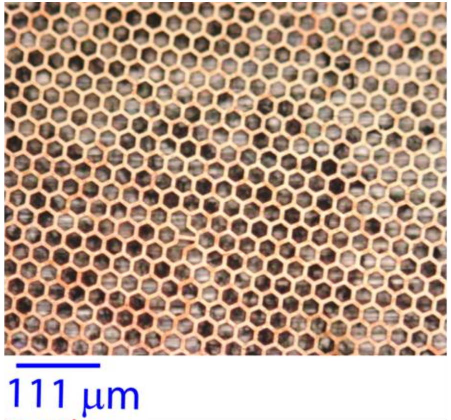
Ang. Chemie. Int. Ed. (2013) **52** 11261-11264

Microscope-based imaging Mass Spectrometry



Courtesy of R, Heeren, Maastricht

Does it really work?

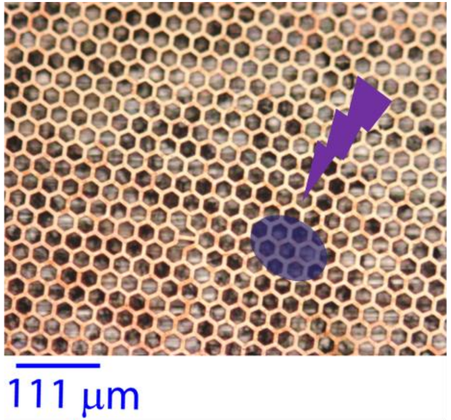


Sample: Protein mix + SA covered with 37 µm TEM grid.

Method: No sample/laser movement during acquisition.
PIE: 0 ns, Lens: 6 kV, EV: 1.68 kV
1000 shots summed

Courtesy of R, Heeren, Maastricht

Does it really work?



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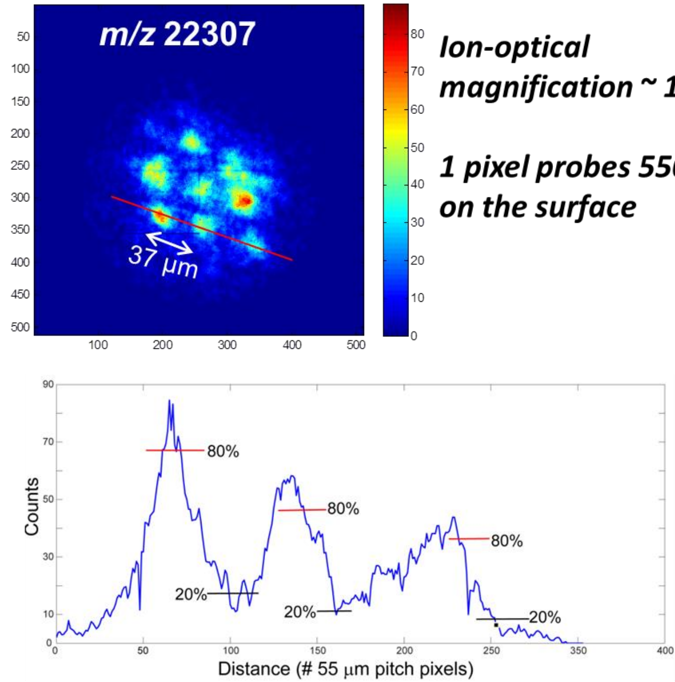
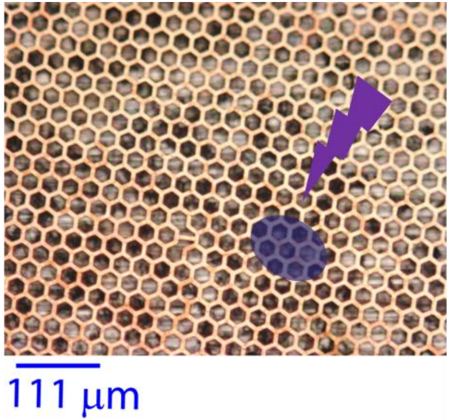


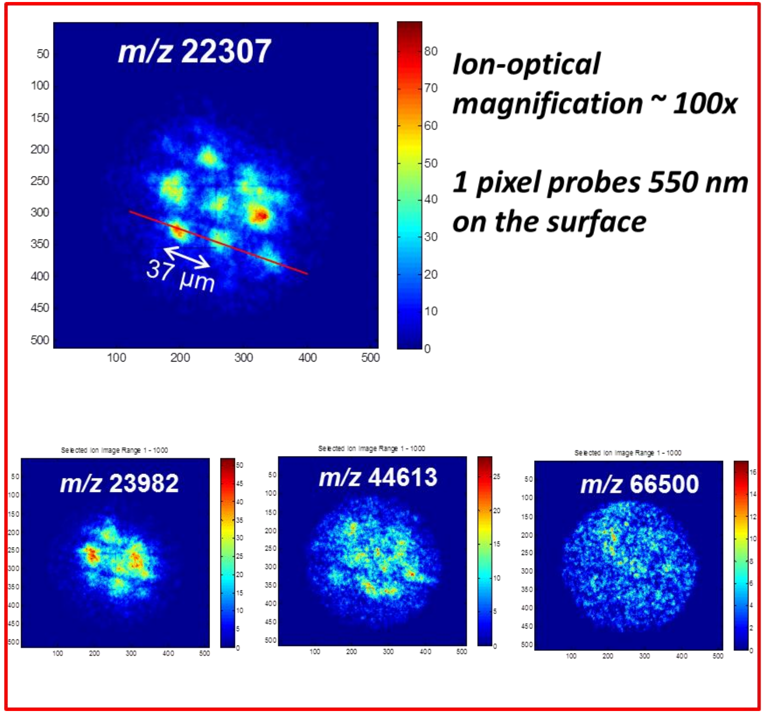
Ion-optical magnification ~ 100x

1 pixel probes 550 nm on the surface

Courtesy of R, Heeren, Maastricht

Does it really work?





Resolution independent of laser spot size and limited only by
-collisions in initial plume
-ion optical abberations
-footprint of single-ion induced electron showers (can be overcome with centroiding approaches)

Courtesy of R, Heeren, Maastricht

Single Layer Compton Camera with MiniPIX TPX3

Compton camera principle

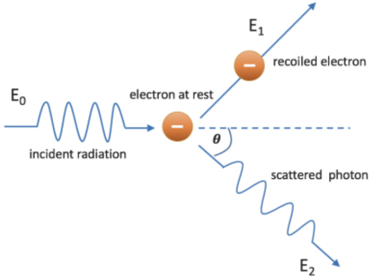
- Typical two detectors
- primary gamma is scattered in first detector (position and energy recorded), scattered gamma continues to second detector (absorbed, position and energy recorded)
- from energies - > scattering angle calculated
- from position and energies -> possible position of the source on the surface of a cone
- Multiple cones intersection - > source position

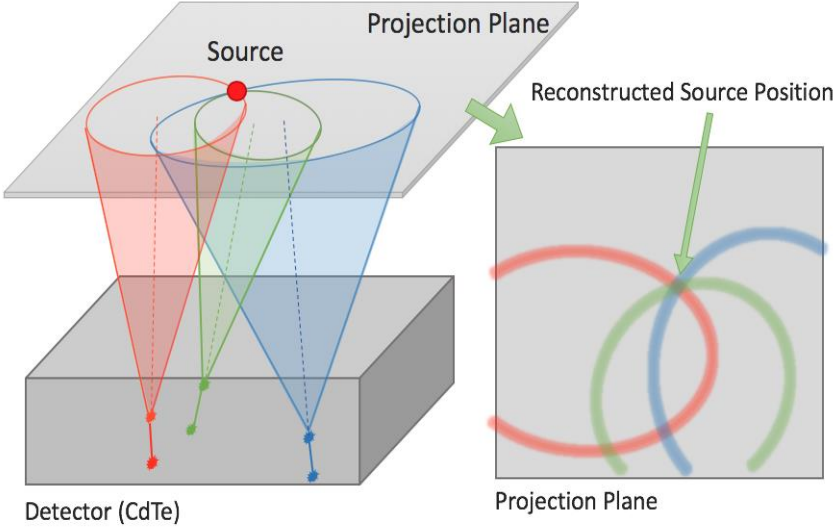
- Single Timepix3 layer camera
  - Instead of 2 detectors, only single TPX3
  - Using time of charge collection to determine relative depth

Courtesy of D. Turecek, Advacam s.r.o

$$\cos\theta = 1 - m_e c^2 \frac{E_1}{E_0(E_0 - E_1)}$$

$$E_0 = E_1 + E_2$$

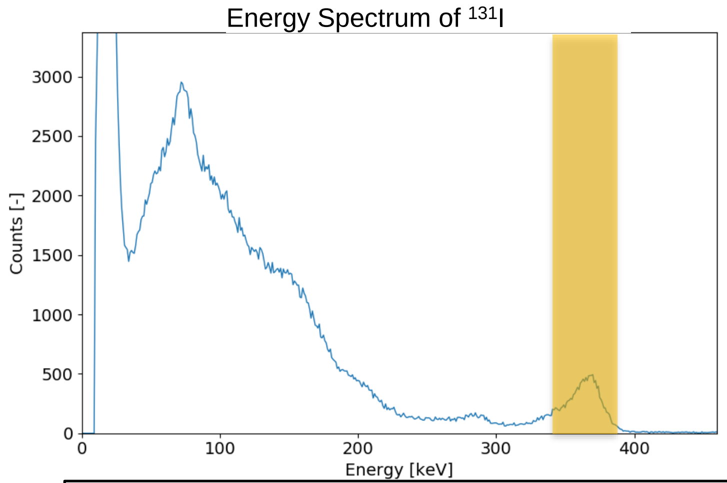




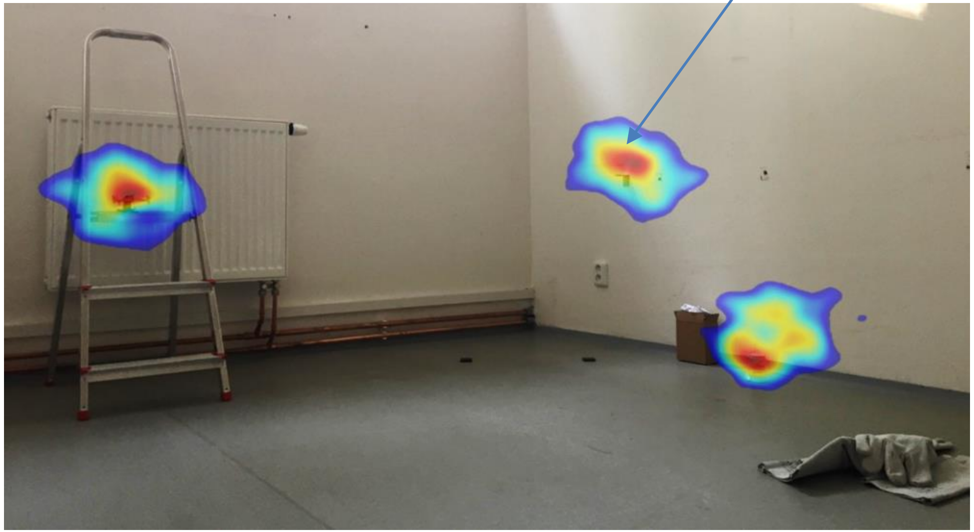
Single Layer Compton Camera with MiniPIX TPX3

^{131}Iodine gamma source

- 3 different Iodine solution in small bottles positioned in a room at different positions
- Distance from detector 3.5 m (activity 10's of MBq)
- Mapped on photograph of the room
- Sources located correctly within minutes
- Image took hours to collect



Courtesy of D. Turecek, Advacam s.r.o

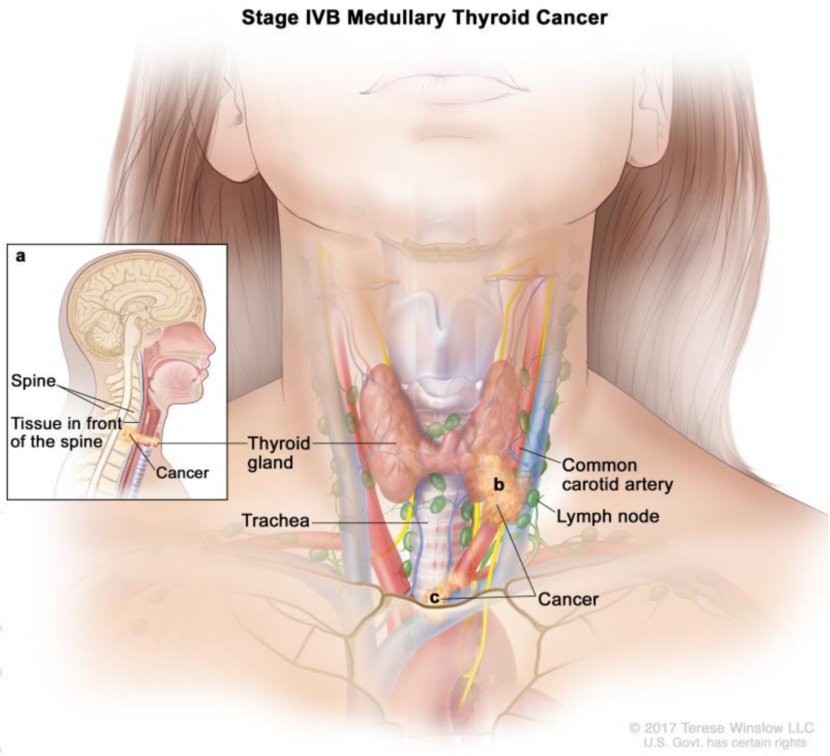


Reconstruction of position of three ^{131}I gamma sources (364 keV)

Gamma camera application: Thyroid diagnostics

Thyroid cancer diagnostics and treatment monitoring:

- The second most frequent cancer for women (after breast cancer)
- Current imaging methods offer resolution of about 12 mm in 2D
- Our technology allows
  - 5 times better resolution and 3D (2.5 mm)
  - 4 times lower dose



Courtesy of D. Turecek, Advacam s.r.o

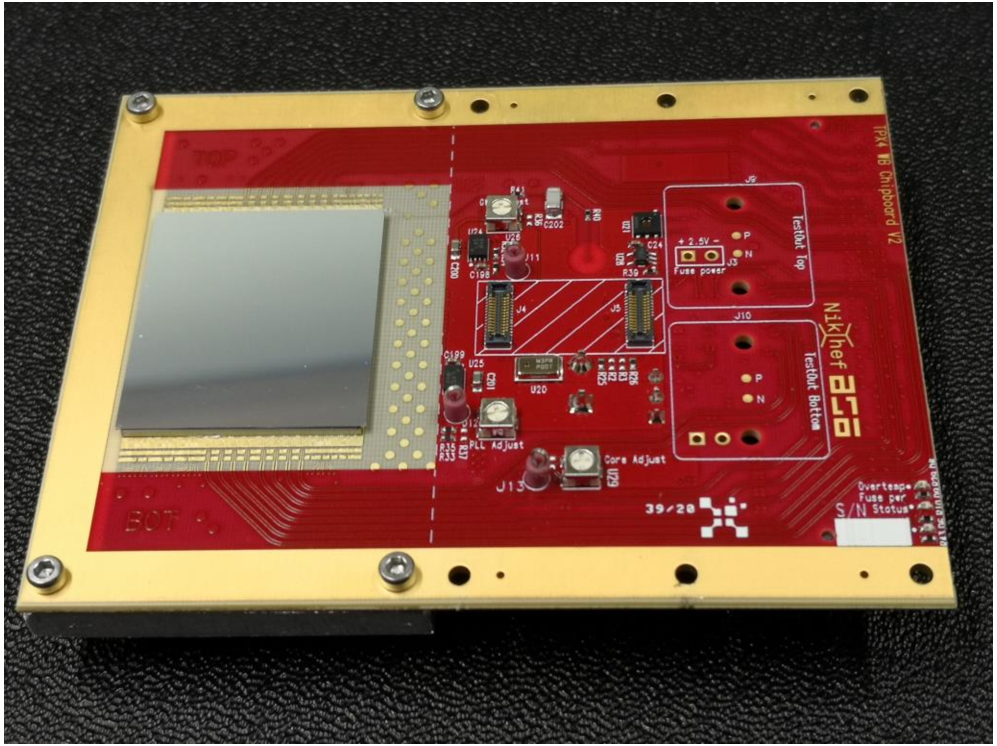
Timepix readout chips - single particle detection

	Timepix	Timepix2	Timepix3
Tech. node (nm)	250	130	130
Year	2005	2018	2014
Pixel size (µm)	55	55	55
# pixels (x x y)	256 x 256	256 x 256	256 x 256
Time bin (bin size in ns)	10	10	1.5
Readout architecture	Frame based (sequential R/W)	Frame based (sequential or continuous R/W)	Data driven or Frame based (sequential R/W)
Number of sides for tiling	3	3	3

Timepix readout chips - single particle detection

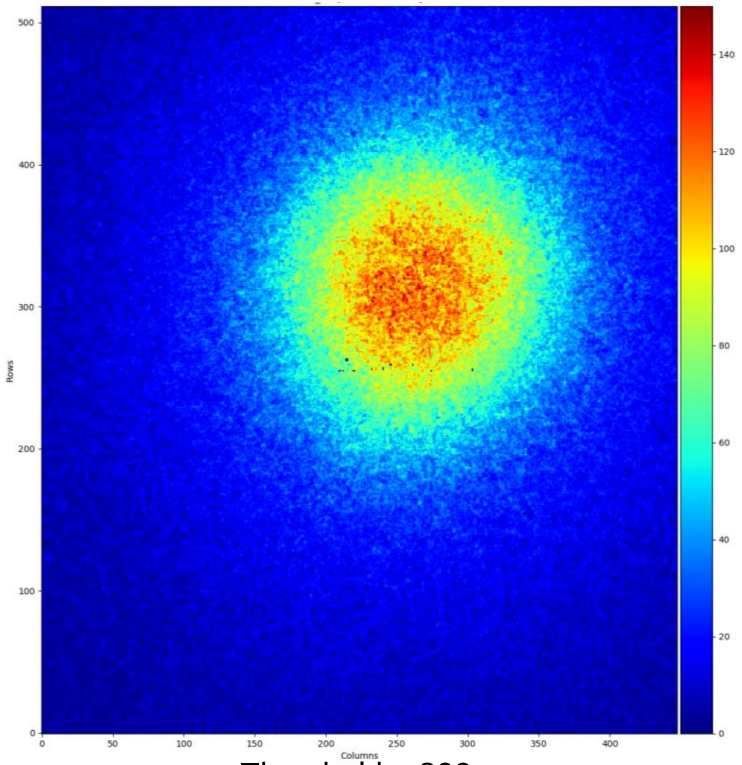
	Timepix	Timepix2	Timepix3	Timepix4
Tech. node (nm)	250	130	130	65
Year	2005	2018	2014	2019
Pixel size (µm)	55	55	55	55
# pixels (x x y)	256 x 256	256 x 256	256 x 256	448 x 512
Time bin (bin size in ns)	10	10	1.5	200ps
Readout architecture	Frame based (sequential R/W)	Frame based (sequential or continuous R/W)	Data driven or Frame based (sequential R/W)	Data driven or Frame-base (sequential or continuous R/W)
Number of sides for tiling	3	3	3	4

Timepix4 – works! ☺



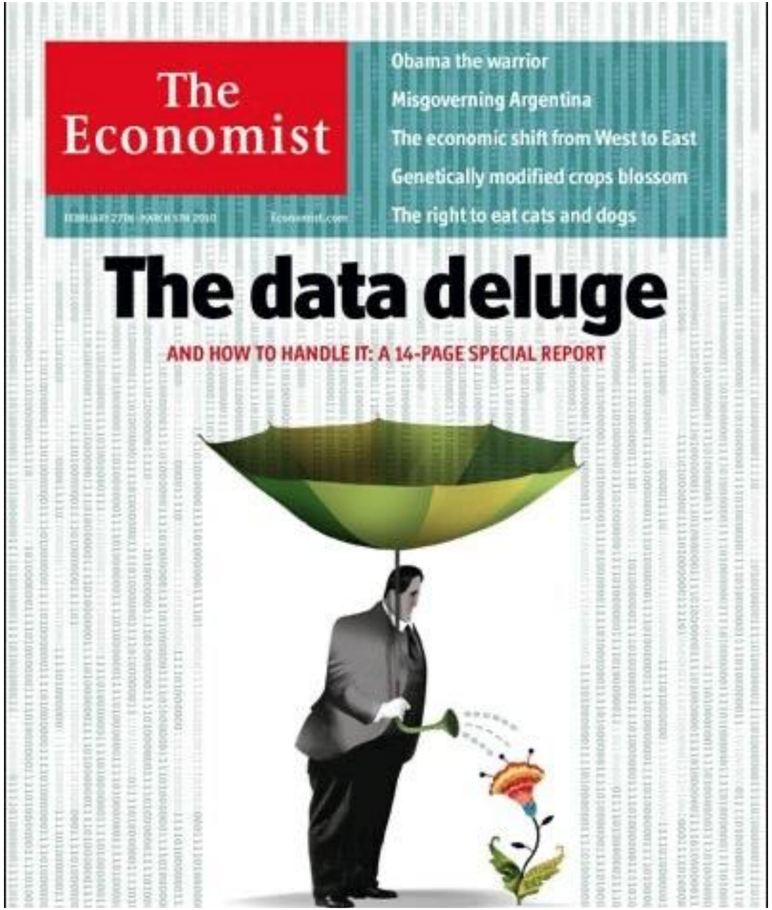
For details see talk of D Pennicard on Monday

10s exp. ^{90}Sr



Threshold ~ 800e$^-$
6.1 M packets @ 5 Gbps

Can be (better) handle the data deluge?



How can 28nm CMOS help (1)?

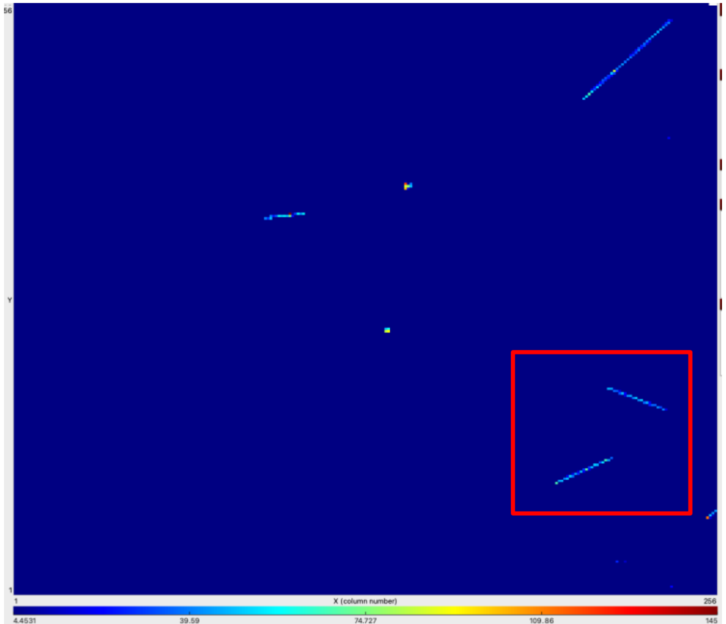
- Increased component density and power efficiency can lead to further improved time-tagging (ultimately limited by the detector) 200ps -> 50ps??

- Can we develop on-pixel logic which helps ‘keep clusters together’?

- Before readout is initiated after, say, 1 clock cycle (or more if needed), a pixel asserts a readout request if and only if it is e.g. the leftmost in a cluster (or alone)

- It the passes the right to be read out (a token) to it’s neighbour(s) to the right

- Only when a full cluster is read out can a new cluster start from a given column



How can 28nm CMOS help (2)?

- Each periphery (or sub periphery) could contain a cluster processor Reduced Instruction Set Computer processor (e.g. RISC -V) and/or CNN(?)
- This processor can be trained/programmed to identify particular cluster shapes: single hits, small clusters, stiff tracks (high p_T), long straight tracks (MIPS, charged particles), long squiggly tracks (electrons), blobs (alphas)
- The processor could be programmed to send out only a subset of information about a given cluster (e.g. timestamp, entry pixel, exit pixel for a MIP; timestamp, entry point, energy(?) for an electron; centre of gravity, total energy for an alpha etc)
- Potential for massive data reduction and ultimate efficiency in use of of-chip bandwidth. Simplified readout even in extreme conditions.

Examples of other applications of Timepix/Medipix

X-rays
- Large area X-ray cameras for synchrotrons
- X-ray materials analysis
- Art authentication
- X-ray non-destructive testing
- X-ray dosimetry - dosepix chip development

Neutrons
- High resolution neutron detection and imaging

Electrons
- Low Energy Electron Microscopy
- Electron Backscattering diffraction (EBSD)

Hadrons
- Dose deposition tracking in hadron therapy

Gammas
- Gamma (and Compton) camera for power plant decommissioning and homeland security

Visible
- Tpix3Cam and 4D photon projects

Mixed field
- Mixed field radiation monitoring on the International Space Station
- Various space weather satellites
- Lunar radiation measurements
- Use in classrooms

Applications for CERN/Physics

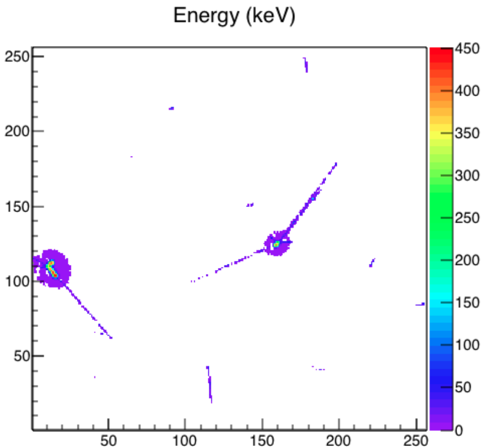
- LHCb VELOpix chip is directly derived from Timepix3
- LHCb Timepix3 telescope – 80 Mhits/cm^2/sec
- Sensor studies for CLIC/LHCb
- Background radiation monitoring at ATLAS and CMS
- Beam monitoring in UA9
- Positron annihilation in Aegis
- ASACUSA experiment
- Beam Gas Interaction real time monitor at SPS
- Breit-Wheeler experiment at RAL
- Beta particle channeling in ISOLDE
- Axion search at CAST (with InGrid)
- Large area TPC (with InGrid)
- Transition radiation measurements for ATLAS
- GEMPIX development for radiation therapy beam monitoring
- GEMPIX for ^{55}Fe waste management
- Developments for CLIC: CLICpix, CLICpix2, C3PD
- Large area dual-phase Li:Ag TPC readout

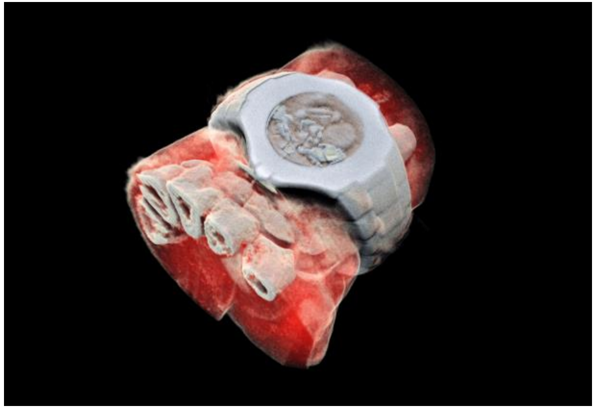
Conclusions

- The Medipix and Timepix chips have been used in multiple applications (both foreseen and otherwise)
- This talk highlighted spectroscopic X-ray imaging, TEM/STEM, Imaging ToF mass spectrometry, SPECT
- Their strength lies in their great versatility (not so ASIC ☺) and a large community of motivated expert researchers and licensees
- The Timepix4 and Medipix4 chips seek to tile large areas seamlessly using TSVs

- We presented some ideas which could go into a future Timepix5 device
  – On pixel clustering
  – On chip particle identification
  – Optimum use of offf-chip bandwidth with much simplified readout
  – Even more programmable and versatile than previous versions.

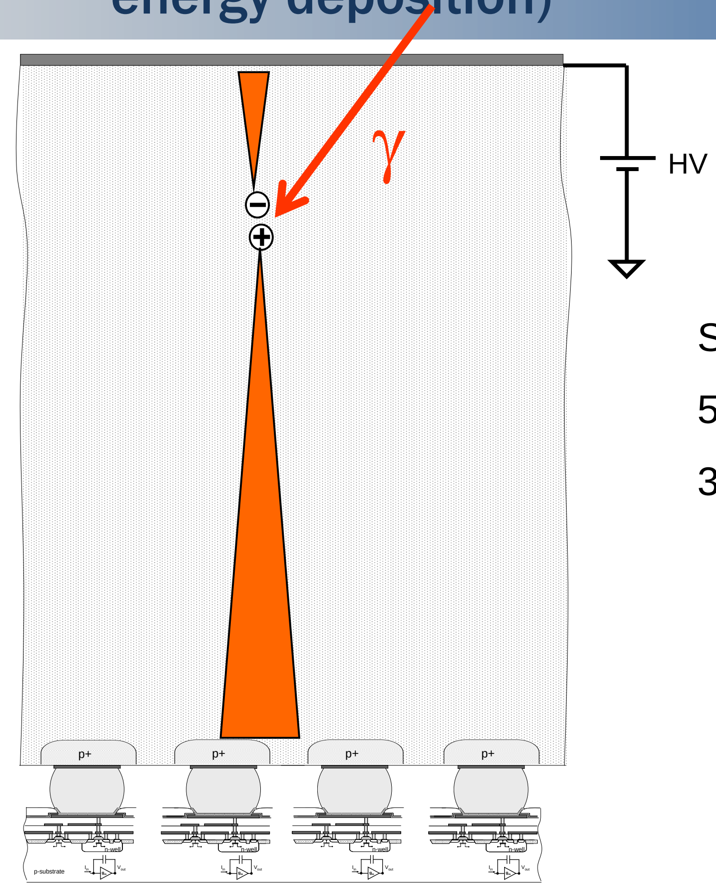
Thank you for your attention!





Backup slides

Cross section of a Hybrid Pixel Detector system (X-ray photon energy deposition)

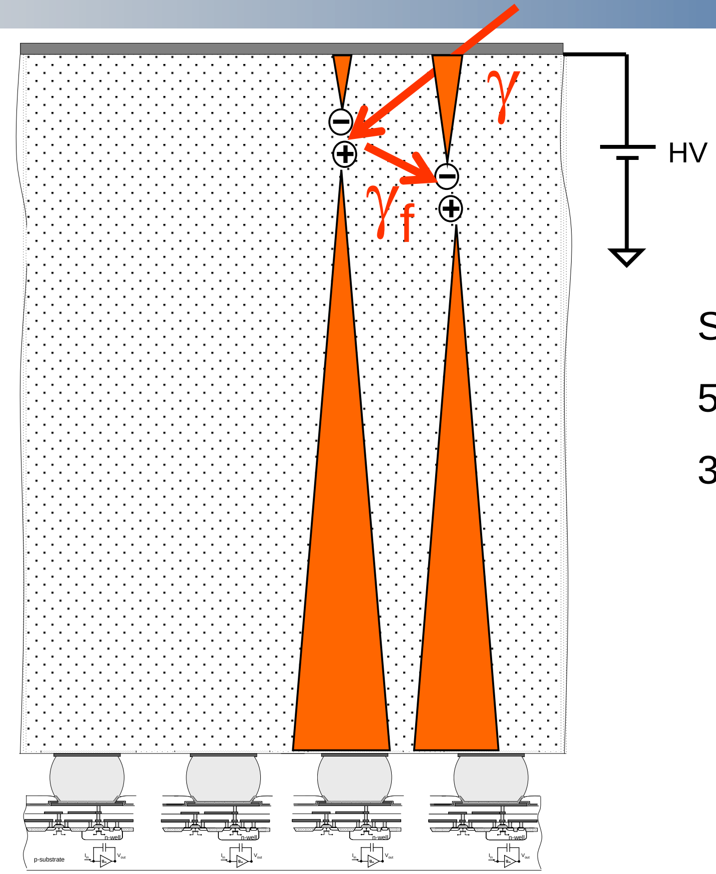


Sensor dimensions to scale:

55μm pixel pitch

300μm thick sensor

Fluorescence in high-Z materials



Sensor dimensions to scale:

55µm pixel pitch

300µm thick sensor

Fluorescence in high-Z detectors

	N	k-edge (keV)	Kα energy (keV)	dα (μm)	η [%]
Si	14	1.84	1.74	12	5
Ge	32	11.11	9.89	51	55
GaAs:					
Ga	31	10.38	9.25	42	51
As	33	11.87	10.54	16	57
CdTe:					
Cd	48	26.73	23.17	128	84
Te	52	31.82	27.47	64	87

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The algorithm for charge reconstruction and hit allocation: Charge Summing Mode